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INTERRELATION BETWEEN EXCRETION OF SEX HORMONES AND THE COPPER, MANGANESE, ZINC AND COBALT CONTENT IN THE PLACENTAS OF WOMEN WITH A NORMAL COURSE AND PREMATURE INTERRUPTION OF PREGNANCY

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INTERRELATION BETWEEN EXCRETION OF SEX HORMONES AND THE COPPER, MANGANESE, ZINC AND COBALT CONTENT IN THE PLACENTAS OF WOMEN WITH A NORMAL COURSE AND PREMATURE INTERRUPTION OF PREGNANCY

[Vzaimootnosheniya mezhdu ekskretsiyey polovykh gormonov i soderzhaniyem medi, margantsa, tsinka, kobal'ta v platsente zhenshchin pri normal'nom techenii i prezhdevre mennom preryvanii beremennosti]

by

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The daily excretion of estrogens and pregnandiol as well as the content of copper, manganese, zinc and cobalt in placental tissue were determined in 63 women with a normal pregnancy and in 92 with spontaneous abortions at different terms of pregnancy. The excretion of estrogens and pregnandiol in the urine in spontaneous abortion is markedly decreased. A maximal level of copper and zinc was found in the chorionic tissue. The content of manganese and cobalt in the placental tissue in the course of pregnancy does not change essentially, whereas in the mature placenta it is significantly reduced. In spontaneous abortion the placental tissue binds copper

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and manganese in an augmented amount and loses zinc and cobalt. The author notes an inverse correlation between the content of copper and estrogen excretion and a direct correlation between the zinc and cobalt level and the excretion of estron, estradiol and estriol.

Trace elements' part in tissue metabolism and their important role in assurring a normal reproductive function allows us to assume the presence of significant changes in the metabolism of these substances in the process of development of normal pregnancy and in premature interruption of it. However research in this area has rarely been conducted on the dynamics of development of pregnancy and as a rule has amounted to determining the content of trace elements in the blood. The question of the interrelationships between the hormone-producing function of the placenta and the level of trace elements in the tissue of this organ remains little studied.

The present article presents results of study of the interconnection between secretion of estrogens and pregnandiol and the copper, manganese, zinc and cobalt content in placental tissue in a normal course and premature interruption of pregnancy.

155 women were examined; they were divided into two groups on the basis of clinical data. The first group included 63 women with a normal course of pregnancy. The term of pregnancy was equal to 6-12 weeks in 20 of them, 14-20 weeks in 16 of them and 21-27 weeks in 27 of them. Their menstrual and parturient functions were not disturbed. Pregnancy proceeded in all of the women without any complications. We obtained the material examined (chorionic and plancental tissue) at a term of pregnancy of from 6 to 12

weeks from women who had come to have an artificial abortion performed. We interrupted pregnancy at terms from 14 to 27 weeks (according to medical indications) through membranous infusion of a rivanol [an antiseptic] solution or a minor cesarean section operation.

Since investigation results did not differ substantially when different methods were used to interrupt pregnancy, the results were consolidated and taken as the arbitrary control.

The second group included 92 women with spontaneous abortions at various terms of pregnancy (30 women at from 6 to 12 weeks, 31 women at from 13 to 20 weeks and 31 women at from 21 to 28 weeks).

This group included patients in whom the supposed cause of interruption of pregnancy was hormone deficiency. 33 of them had had spontaneous abortions in the past; 16 women had habitual miscarriages. Disturbances of the menstrual cycle were noted in 42 of the women prior to pregnancy.

The patients entered the clinic with abortion threatening or begun. Women in whom pregnancy was preserved were excluded from investigation, as were patients with miscarriages taking place before the daily urine sample was completed. The placental stage proceeded without complications in all cases of late miscarriage.

Injury to vitally important organs, as well as acute or chronic infectious diseases, were absent in all examinees. No deviations from the norm were discovered in clinical and

laboratory examination. Neither before nor during examination did the women receive hormone preparations that might have influenced the results of the investigation. We conducted the daily urine sample to determine excretion of sex hormones before interruption of pregnancy; we took the placenta for investigation immediately after birth.

We assessed the hormone-producing function of the placenta according to the level of excretion of estrogens and pregnandiol with urine. We determined the amount of estrogens in the daily urine according to fractions by the Brown method and that of pregnandiol, after Klopper. We determined the copper and manganese content in the ashes of placental tissue by the emission spectral analysis method; the cobalt content colorimetrically after G. A. Babenko; and the zinc content, by the polarographic method. We calculated the amount of trace elements per 100 g of wet tissue weight. The results were processed by the variational statistics method.

The research conducted showed that development of pregnancy is accompanied by a sharp increase in elimination of estrogens in the urine (see Table). The amount of excreted estriol increases especially rapidly: as compared with 6-12 weeks of pregnancy, excretion of it increases 15 times at a 14-20 week term and 32 times at a 21-27 week term. Excretion of estrone increases 4.6 and 9.2 times respectively and that of estradiol, 3.8 and 7.1 times.

Table. Excretion of estrogens (in μg/day) and pregnandiol (in mg/day) in the urine in a normal course and premature interruption of pregnancy (M ± m).

Течение беременности (a)	Срок беременности (в неделях) (b)	Число наблюдений (c)	Эстрогены (d)			Прегнандиол (h)
			эстрон (e)	эстрадиол (f)	эстриол (g)	
(i) Нормальное	6—12	20	48±4,2	16±2,0	169±22	13,3±1,2
	14—20	16	224±35,7	60±5,3	2 425±257	22,9±2,4
	21—27	16	443±55,0	113±13,6	5 363±432	30,0±2,1
(j) Самопроизвольный аборт	6—12	28	12±2,4	4±0,8	47±7,9	4,5±0,7
	13—20	27	53±9.2	14±2,5	427±96	9,2±1,5
	21—28	25	135±17,5	34±4,3	1 484±300	13,8±1,8

Key: a. course of pregnancy; b. term of pregnancy (in weeks); c. number of observations; d. estrogens; e. estrone; f. estradiol; g. estriol; h. pregnandiol; i. normal; j. spontaneous abortion.

Excretion of pregnandiol is already rather considerable (13.3 ±1.2 mg/day) at 6-12 weeks of pregnancy. Subsequently excretion of it gradually increases and at a term of 14-20 weeks exceeds the preceding level 1.7 times and at a term of 21-27 weeks exceeds it by 2.3 times. Inasmuch as the rate of increase in estrogen excretion is considerably higher in the process of development of pregnancy than the rate of increase in pregnandiol excretion, the ratio of total estrogens to pregnandiol equals 1 : 56 at a 6-12 week term of pregnancy and amounts to 1 : 9 at a 14-20 week term and 1 : 5 at a 21-27 week term.

A sharp decrease in daily excretion of all three estrogen fractions is discovered in spontaneous interruption of pregnancy.

As can be seen from the table, excretion of all estrogen fractions decreases an average of 3.5-4 times as compared with the norm in miscarriage at a term of 6 to 12 weeks. In miscarriage occurring at a term of pregnancy of from 13 to 28 weeks, excretion of estrone and estradiol decreases 3.3-4.3 times and that of estriol, 3.6-5.8 times. The differences revealed are statistically reliable ($P < 0.001$).

The amount of excreted pregnandiol proved considerably reduced in spontaneous abortion. In miscarriage at a term of from 6 to 12 weeks pregnandiol excretion decreased 2.9 times, from 13 to 20 weeks it decreased 2.5 times and from 21 to 28 weeks it decreased 2.2 times as compared with excretion of the metabolite at analogous terms in a normal pregnancy ($P < 0.001$).

More detailed analysis of the data obtained showed that secretion of estrogens (especially estradiol) decreases most sharply in spontaneous abortion. In this obstetric pathology, pregnandiol excretion drops below the minimum level observed in a normal pregnancy in 2/3 of the women examined.

As a result of the investigation, certain regularities were also established in change in the trace element content in the chorionic and plancental tissue during development of a normal pregnancy. The greatest amount of copper is discovered in chorionic tissue at 6-12 weeks of pregnancy (167 ± 11.3 µg%). A sharp drop in the copper content is noted upon completion of formation of the placenta ($P < 0.001$). However the amount of copper in placental tissue again increases when labor begins

($P < 0.05$). The greatest zinc content in the chorion is also revealed in the first third of pregnancy (708 ± 43 µg%). Subsequently it gradually decreases and the zinc level is lower in a mature placenta than at 6-12 weeks of pregnancy. The manganese content in placental tissue is relatively low (2.3-3.1 µg%). We did not discover a marked change in its content in the placenta at various terms of pregnancy. At the onset of labor the amount of manganese in placental tissue is reduced still more ($P < 0.001$). The cobalt content in placental tissue is practically identical at different terms of pregnancy (7.1-8.8 µg%). In a mature placenta, the amount of it drops sharply ($P < 0.001$).

The changes in the trace element content in the placental tissue discovered in spontanous abortion are highly significant. An increased amount of copper was revealed in placental tissue in this pathology, especially in miscarriage occurring in the first 20 weeks of pregnancy ($P < 0.001$). The manganese content in miscarriage occurring at 6-12 weeks of pregnancy was 1.9 times higher, at 13-20 weeks 3 times higher and at 21-28 weeks, 4.2 times higher than in placental tissue at the same term of a normal pregnancy ($P < 0.001$). The level of zinc in placental tissue was reduced as compared with the norm ($P < 0.001$) in spontaneous abortion occurring at a term of pregnancy of from 6 to 28 weeks. Moreover, a sharp decrease (1.9-2.7 times) as compared with the norm was revealed in the cobalt content.

A statistically significant inverse correlation ($r = -0.633$, $P < 0.001$) between excretion of total estrogens and the level of

copper in placental tissue has been established in an uncomplicated course of pregnancy. The inverse correlation between excretion of estriol and the copper content in placental tissue ($r = -0.622$, $P < 0.001$) also proved substantial. A statistically significant direct correlation ($r = +0.534$, $P < 0.001$) was discovered between excretion of pregnandiol and the copper level in placental tissue.

The correlative dependence between the manganese content and excretion of total estrogens ($r = +0.342$, $P < 0.02$) and estriol ($r = +0.348$, $P < 0.02$) also proved statistically reliable. A direct correlation between the amount of cobalt in placental tissue and excretion of total estrogens ($r = +0.308$, $P < 0.05$) and estriol ($r = +0.310$, $P < 0.05$) was revealed.

Therefore correlative links have been revealed between excretion of estrogen hormones and pregnandiol and the copper, manganese and cobalt concentration in placental tissue in the physiological course of pregnancy.

The statistically significant inverse correlative link between the copper concentration in the placental tissue and excretion of total estrogens ($r = -0.333$, $P < 0.01$) and estriol ($r = -348$, $P < 0.01$) and the direct correlation between the level of trace elements and pregnandiol excretion ($r = +0.290$, $P < 0.05$) is preserved in spontaneous abortion.

As has already been demonstrated, placental tissue binds copper and manganese in a heightened amount in spontanous abortion and simultaneously loses zinc and cobalt. It was natural to

suppose that the differences in the levels of the trace elements studied in a normal course and premature interruption of pregnancy are linked with various hormone-producing activities of the placenta (and with the estrogen-producing activity first of all). Secretion of various estrogen fractions and the trace element content were compared in order to check this hypothesis. Comparison was conducted in a normal course and premature interruption of pregnancy at analogous terms (6-12, 13-20 and 21-28 weeks) and the degree of correlation of indices being compared was calculated.

The presence of a statistically significant inverse correlation between excretion of all estrogen fractions and the level of copper in placental tissue in the first 20 weeks of an uncomplicated and spontaneously interrupted pregnancy was established as a result of the investigations (r varied from -0.331 to -0.540 at $P < 0.05$-0.01). A direct, reliable correlative link was discovered between excretion of estrone, estradiol and estriol and the zinc concentration in placental tissue at a term of from 6 to 28 weeks in a physiologically proceeding pregnancy and one complicated by abortion (r is within +0.375 to +0.634 at $P < 0.05$-0.001). A direct and statistically substantial link between excretion of all estrogen fractions and cobalt content in the placenta (r varied from +0.358 to +0.634, $P < 0.02$-0.001) was established in these same clinical conditions. Therefore the data obtained testify that the differences in the copper, zinc and cobalt levels in women with normal and prematurely interrupted pregnancies are linked with the differing estrogen-producing

activity of the placenta.

It is known that copper is part of some enzymes that bring about processes of biological oxidation (for example, cytochrome oxidase) while zinc is a structural component or specific activator of many dehydrogenases participating in synthesis of proteins, steroids, lipoids etc. (V. Z. Gorkin; G. A. Babenko; Wallee et al). From this point of view the differences in the level of trace elements in a normal and prematurely interrupted pregnancy may be explained by peculiarities of metabolism in placental tissues. In particular, in spontaneous miscarriage the pattern of bioenergetic metabolism of placental tissue evidently changes in the direction of heightened oxidation processes with simultaneous decrease in the intensity of synthesis of steroids, proteins and other substances. This is probably a compensatory reaction aimed at better adaptability of the placenta to unfavorable conditions that have arisen.

The data obtained allow us to conclude that the spectrum of trace elements in the placenta is linked with its hormone-producing activity and with peculiarities of the bioenergetics of placental tissue in a normal and complicated course of pregnancy.

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